

# 2-Arylacetamides as Versatile Precursors for 3-Aminoisocoumarin and Homophthalimide Derivatives: Palladium-Catalyzed Cascade Double Carbonylation Reactions

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**Abstract:** The synthesis of biologically relevant homophthalimide and 3-aminoisocoumarin nuclei *via* palladium-catalyzed carbonylation of 2-(2-iodoaryl)acetamides has been developed. The degree of N-substitution on the starting amide substrate dictates whether C–N or C–O coupling takes place in the final step of the catalytic cycle giving rise to each type of heterocycle. The introduction of a second C–halogen bond in the starting acetamides allows a catalytic cascade double carbonylation involving a C–H activation step to give fused heterocyclic structures.

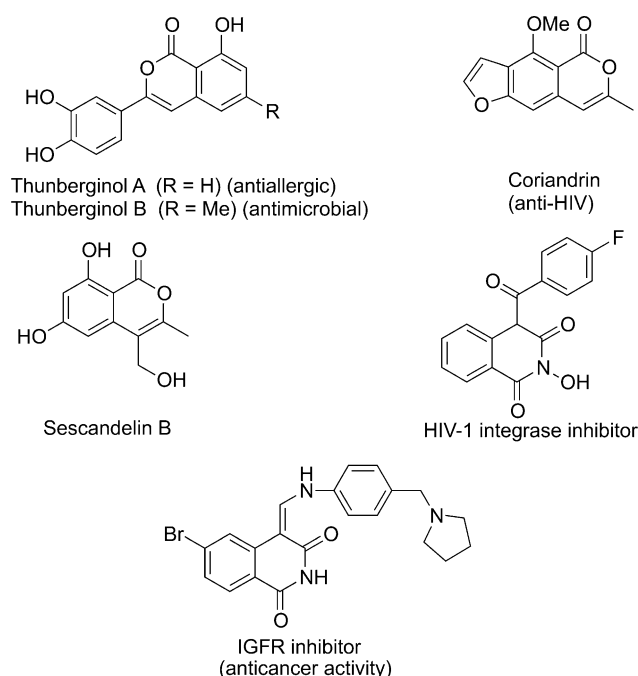
**Keywords:** carbonylation; cascade reactions; C–H functionalization; heterocycles; palladium

Isocoumarin and homophthalimide nuclei are privileged six-membered O- and N-heterocycles, respectively, with a widespread presence in biologically active compounds exhibiting antifungal,<sup>[1]</sup> anti-inflammatory,<sup>[2,3]</sup> and cytotoxic activities,<sup>[4,5]</sup> among many others.<sup>[6,7]</sup> They are also present in the core of natural products such as sescandelin B or phelligradin D (Scheme 1).

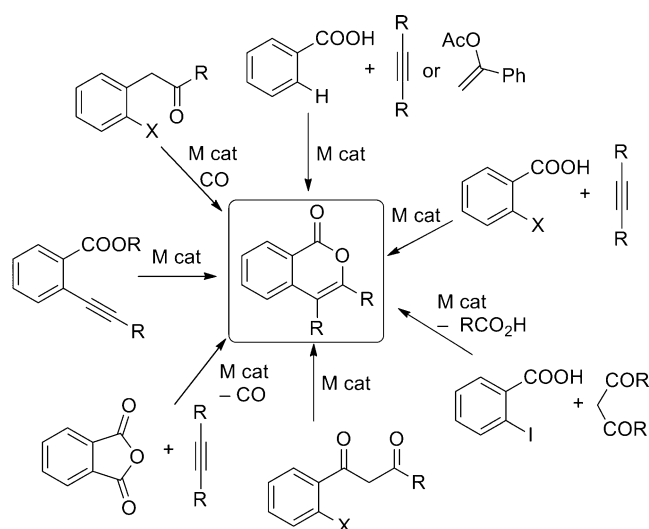
In the last decades there has been a considerable effort to develop new and efficient synthetic routes to obtain these types of scaffolds with different substitution patterns. The main methods to synthesize isocoumarins involve the cyclization of 1,2-difunctionalized arenes (including *ortho*-alkynylbenzoic,<sup>[8]</sup> 2-halobenzoate<sup>[9,10]</sup> or phthalic anhydride derivatives<sup>[11]</sup>) with coupling partners such as alkynes or CO (Scheme 2).<sup>[12,13]</sup> Lately, transition metal-catalyzed carboxylate-directed *ortho* C–H activation of benzoic acid derivatives has emerged as an interesting approach to isocoumarins.<sup>[14,15]</sup> All these methodologies

give rise to 3,4-alkyl-, aryl-, alkoxy-, acyl- and ester-substituted isocoumarins.

The presence of heteroatomic substituents in biologically relevant scaffolds might confer new properties or applications to these compounds. Therefore new synthetic methodologies with the aim of introducing O,<sup>[16]</sup> S,<sup>[17]</sup> I,<sup>[18–20]</sup> Br, Cl,<sup>[19]</sup> Se,<sup>[18]</sup> or Si<sup>[11]</sup> substituents in the isocoumarin core are being developed. Only a few papers on the introduction of N-substituents in the 3 or 4 positions of the isocoumarin scaffold have been published.<sup>[7,21]</sup> Among them, there is a multicomponent Ugi reaction involving the coupling of 2-formylbenzoic acid, an amine and an isocyanide



**Scheme 1.** Examples of biologically active or natural compounds containing the isocoumarin or homophthalimide structural motif.



**Scheme 2.** Main routes for the synthesis of isocoumarins.

giving rise to 3,4-diamino-substituted isocoumarins as the primary adduct.<sup>[21]</sup>

In contrast to isoquinolones, the synthesis of the structurally related homophthalimides (1,3-isoquinolinediones) has received considerably less attention, in spite of their presence in biologically important compounds. Homophthalimides are mainly obtained by reaction of an amine with homophthalic acid<sup>[22]</sup> or anhydride derivatives.<sup>[2,23,24]</sup>

The functionalization of 2-arylacetic acids or amides through transition metal-catalyzed C–H activation is an attractive route that has been successfully applied to their arylation,<sup>[25,26]</sup> alkenylation,<sup>[26]</sup> acetoxylation,<sup>[27]</sup> and halogenation.<sup>[28]</sup> Nevertheless only a few examples of transition metal-catalyzed carbonylation reactions of these substrates *via* C–H activation have been reported, requiring harsh conditions (both high temperature and catalyst loading)<sup>[29]</sup> or the use of a bidentate directing group to facilitate the C–H activation step.<sup>[30]</sup> Hence, 2-haloarylacetamides might be worthy complementary substrates in these carbonylation reactions.

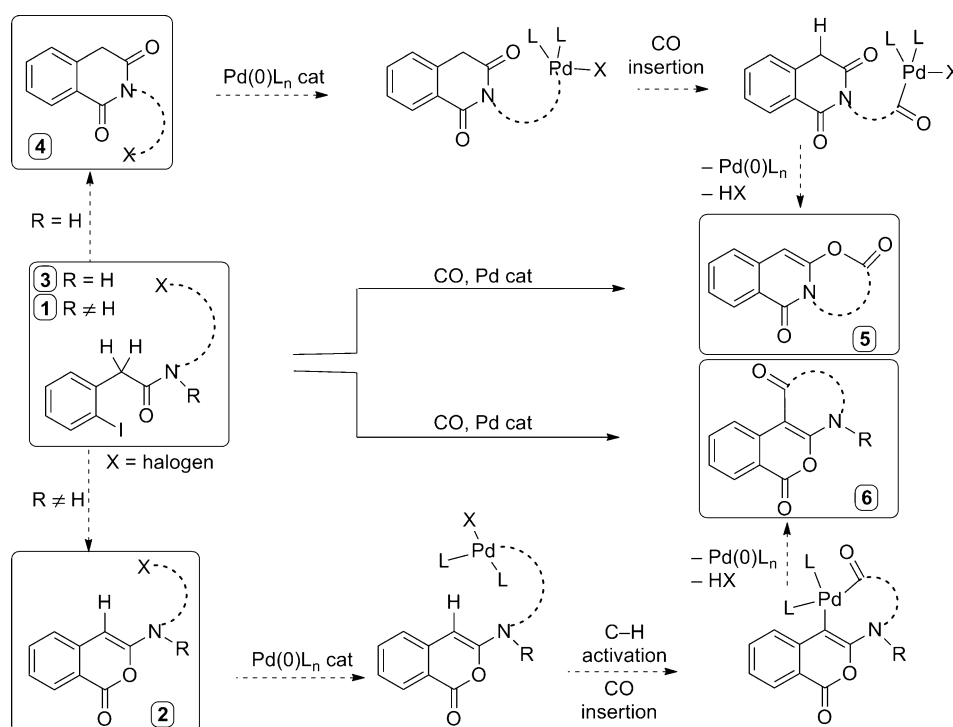
Our research group has been interested in the study of the reactivity of cyclopalladated complexes toward CO.<sup>[31]</sup> Thus, we reported recently the carbonylation reaction of cyclopalladated arylacetamide complexes.<sup>[32]</sup> In the stoichiometric model, the nature of the starting amide dictated the outcome of this reaction. When the substrate contained an NH<sub>2</sub> or NHR group, the intermediate acyl-palladium complex underwent a reductive elimination with subsequent C–N bond formation to give the corresponding homophthalimide derivative. Remarkably, when tertiary amides were employed instead, the C–O bond formation took place preferentially upon enolization of the acidic alpha CH<sub>2</sub> group, affording 3-aminoisocoumarins.

Catalytic cascade reactions have gained attention in recent years since they allow the construction of complex molecular structures from simple substrates in a straightforward and efficient manner.<sup>[33]</sup> In these processes the initial transformation of a conveniently designed substrate affords a new structural motif which is, in turn, susceptible to undergo a further functionalization carried out by the same catalytic system. Cascade reactions become especially relevant when they involve C–H activation processes in some or all of their steps because they improve the overall atom-economy of the synthesis.<sup>[34]</sup> We envisioned that the introduction of a pendant reactive site in the nitrogen atom of the starting 2-arylacetamide could give rise to structures primed for cascade Pd-catalyzed carbonylation processes (such as those depicted in the Scheme 3) based on the initial production of either homophthalimide or isocoumarin cores.

Hence, in this contribution we report the synthesis of both homophthalimides and 3-aminoisocoumarins from 2-(2-haloaryl)acetamides in a catalytic fashion, as well as the development of catalytic cascade double carbonylation reactions from the appropriate 2-arylacetamide derivatives achieving interesting fused heterocyclic scaffolds.

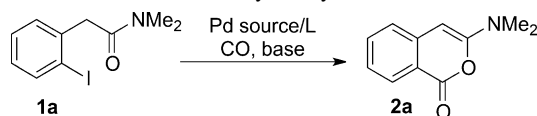
We started our study by attempting the carbonylation reaction of 2-(2-iodophenyl)-*N,N*-dimethylacetamide (**1a**) using Pd(dba)<sub>2</sub> as the Pd(0) source and TMEDA as base/ligand (entry 1, Table 1). These conditions did provide the expected isocoumarin **2a**, albeit in a low yield. After a short optimization process, the yield was improved to nearly full conversion of the starting material by generating Pd(0) *in situ* from simple Pd(OAc)<sub>2</sub> (5 mol%) and PPh<sub>3</sub> (20 mol%) in either dry toluene or 1,4-dioxane at 100 °C (entries 3 and 7, Table 1). Lower temperatures or catalyst loadings decreased the performance of the catalytic carbonylation (entries 4, 5 and 6, Table 1). Although the NMR yield for the 3-dimethylaminoisocoumarin **2a** was good, it proved to be sensitive to purification by flash column chromatography on silica gel, probably due to hydrolysis processes leading to the opening of the heterocyclic structure. The use of neutral alumina improved the efficiency of the chromatographic purification, furnishing a 51% isolated yield of isocoumarin **2a**.

A range of 2-(2-iodophenyl)-*N,N*-disubstituted acetamides **1a–g** were submitted to the carbonylation conditions, giving rise to the 3-substituted isocoumarins **2a–g** (including cyclic amines as substituents such as piperidine and morpholine) in moderate isolated yields (Scheme 4). The extension of the reaction scope to other heteroatom-containing substrates was performed by using the ester **1h** and the thioester **1i** as starting materials, which provided the corresponding 3-*O*- and 3-*S*-substituted isocoumarins **2h** and **2i** in moderate yield. The attempts to replace the iodi-



**Scheme 3.** Proposed catalytic cascade double carbonylation reactions from 2-arylacetamides.

**Table 1.** Screening of the reaction conditions for the Pd-catalyzed synthesis of isocoumarin **2a**.<sup>[a]</sup>



Entry	Pd source (mol%)	Ligand (mol%)	Base (equiv.)	Yield [%] <sup>[b]</sup>
1	Pd(dba) <sub>2</sub> (5)	–	TMEDA (1.2)	10
2	Pd(dba) <sub>2</sub> (5)	TMEDA (10)	K <sub>2</sub> CO <sub>3</sub> (1)	80
3	Pd(OAc) <sub>2</sub> (5)	PPh <sub>3</sub> (20)	K <sub>2</sub> CO <sub>3</sub> (1)	95
4	Pd(OAc) <sub>2</sub> (2.5)	PPh <sub>3</sub> (10)	K <sub>2</sub> CO <sub>3</sub> (1)	90
5	Pd(OAc) <sub>2</sub> (1)	PPh <sub>3</sub> (4)	K <sub>2</sub> CO <sub>3</sub> (1)	78
6 <sup>[c]</sup>	Pd(OAc) <sub>2</sub> (5)	PPh <sub>3</sub> (20)	K <sub>2</sub> CO <sub>3</sub> (1)	12
7 <sup>[d]</sup>	Pd(OAc) <sub>2</sub> (5)	PPh <sub>3</sub> (20)	K <sub>2</sub> CO <sub>3</sub> (1)	96 (51) <sup>[e]</sup>

<sup>[a]</sup> Reactions carried out using substrate **1a** (0.6 mmol), dry toluene (3 mL) and CO (1.2 atm.) in a Carius tube at 100°C.

<sup>[b]</sup> NMR yields.

<sup>[c]</sup> Reaction carried out at 50°C.

<sup>[d]</sup> Dry 1,4-dioxane (3 mL) was used as the solvent.

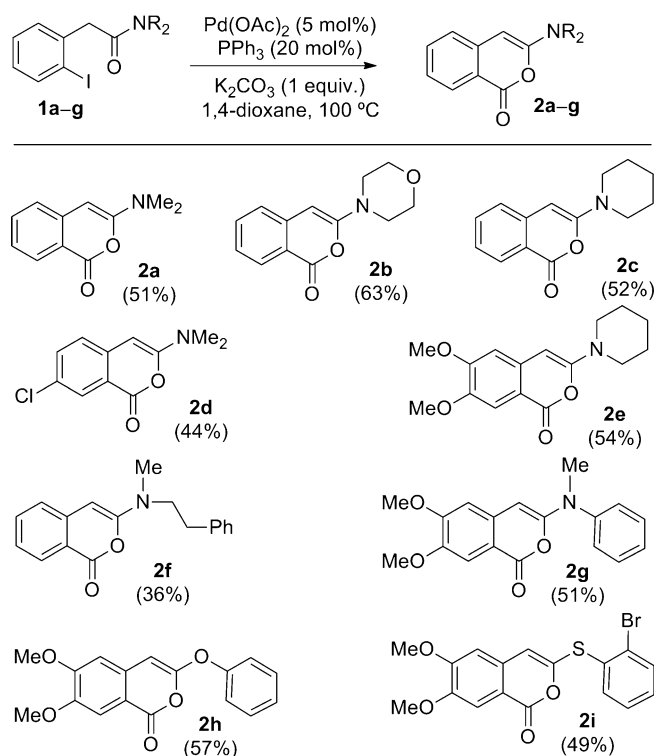
<sup>[e]</sup> Isolated yield after column chromatography.

<sup>[f]</sup> TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

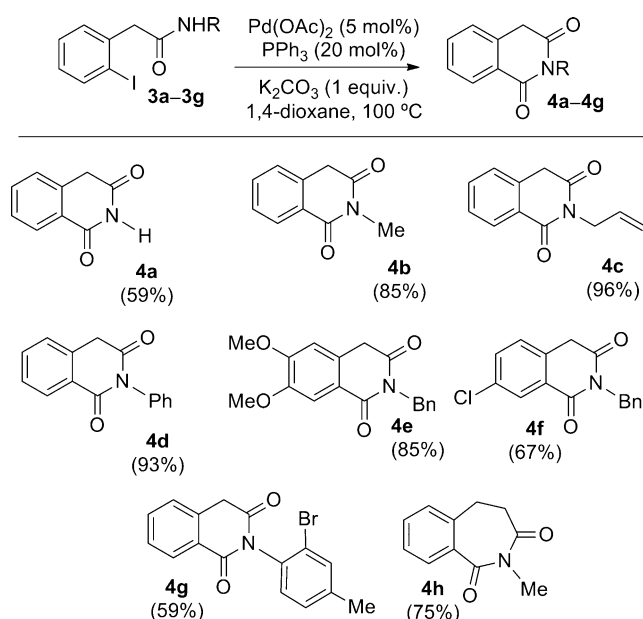
nated substrates **1** for the cheaper but more challenging chlorinated analogues proved unfruitful even on heating up to 140°C or using the Buchwald's precatalyst as the palladium source.<sup>[36]</sup>

We then turned our attention to unsubstituted or *N*-monosubstituted 2-arylacetamide substrates **3a–3g**. As stated in our previous stoichiometric study,<sup>[32]</sup> the palladium-catalyzed carbonylation of these substrates led to the formation of homophthalimides **4a–4g** in good yields (Scheme 5). The reaction tolerates well

alkyl, allyl and aryl substituents on the nitrogen atom, as well as the presence of electron-donating or electron-withdrawing groups in the aromatic ring. The presence of a bromine atom in the *N*-aryl substrate **3g** was tolerated under the reaction conditions, obtaining a 59% yield of the homophthalimide **4g**. The method could be extended to the synthesis of the 7-membered benzazepin-1,3-dione **4h** in good yield by using *N*-methyl-3-(2-iodophenyl)propanamide as starting material.<sup>[35]</sup>



**Scheme 4.** Scope on 3-*N*-, *O*- and *S*-substituted isocoumarins.

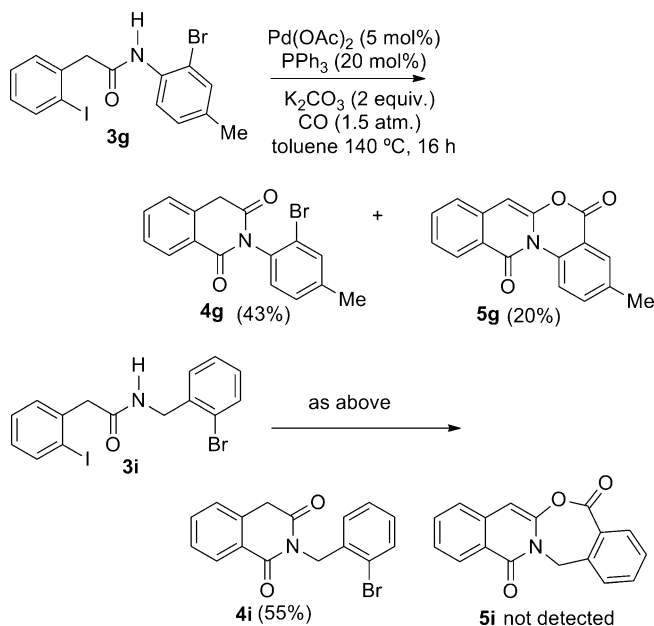


**Scheme 5.** Scope of the synthesis of homophthalimides.

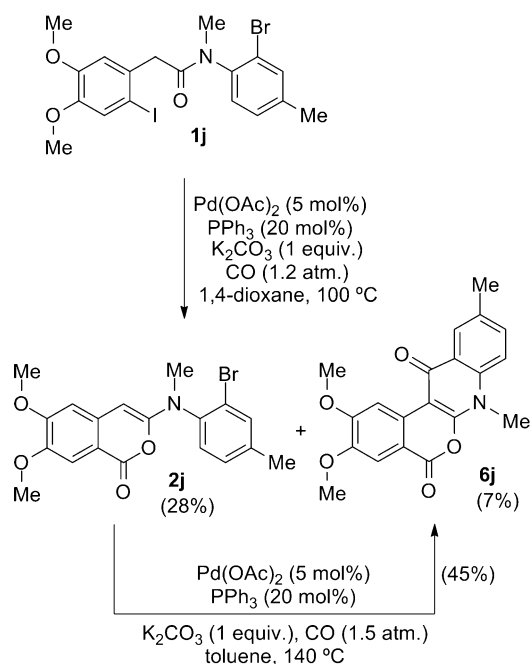
With these reaction conditions in hand, we decided to explore the use of 2-(2-iodoaryl)acetamides for the development of catalytic cascade carbonylation processes. We reasoned that the cascade cyclization leading to the fused heterocyclic systems **5** and **6** (Scheme 3) could be successful when the tethering

chain on the nitrogen atom fulfilled two conditions: first, it should contain a reactive site which should not hamper the initial oxidative addition of the C–I bond to Pd(0) (in order to render the desired homophthalimide/isocoumarin intermediate); and second, the length of the tethering chain should be appropriate to place the Pd atom in close proximity to the homophthalimide or isocoumarin core, allowing the cyclization step to occur. We chose the 2-bromoaryl moiety as a suitable substituent on the nitrogen atom of the amide. The C–I bond present in the aryl substrates undergoes a faster oxidative addition to Pd(0) compared to the C–Br bond, hence the later would not represent a significant competitor in the first step of the reaction, minimizing the generation of by-products. Moreover, the oxidative addition of palladium to the C–Br bond of the resulting *N*-aryl-substituted isocoumarins **2** or homophthalimides **4** (Scheme 3), would lead to suitable six-membered palladacycles where CO insertion and oxidative cyclization are possible, as demonstrated in stoichiometric models of similar size.<sup>[31a,d,32]</sup>

We had observed that the *N*-aryl-substituted acetamide **3g** (bearing the bromine atom) afforded the homophthalimide **4g** in good yield. Hence we attempted harsher conditions in order to make it further react. The desired fused heterocycle **5g** was indeed formed when the reaction was performed in dry toluene at 140 °C, albeit in a low 20% yield (Scheme 6). Unfortunately, the change of other reaction parameters such as the base (*t*-BuOK), catalyst loading (increased to 10%), reaction times (up to 24 h) or the palladium(0) source (Buchwald's precata-



**Scheme 6.** Attempted catalytic double carbonylation of homophthalimide derivatives.

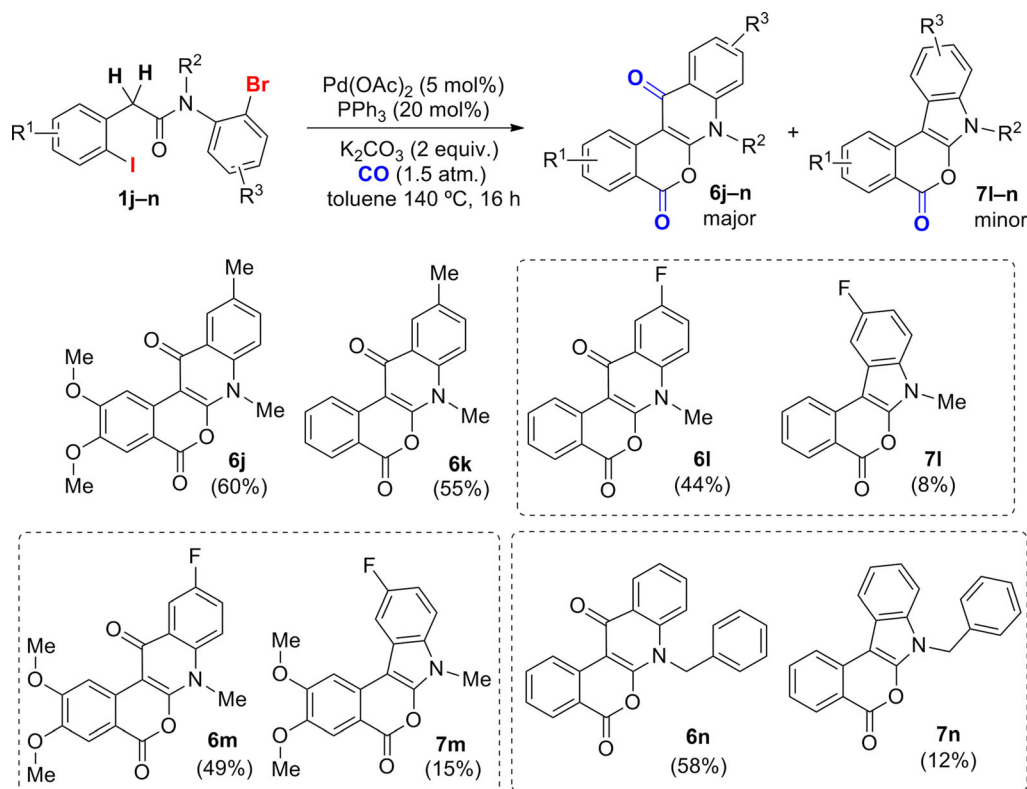


**Scheme 7.** Synthesis of the fused heterocycle **6j** from **1j** and **2j**.

lyst)<sup>[36]</sup> did not improve the formation of **5g**. The double carbonylation was also unsuccessful with the substrate **3i** bearing a 2-bromobenzyl substituent on the nitrogen atom (Scheme 6).

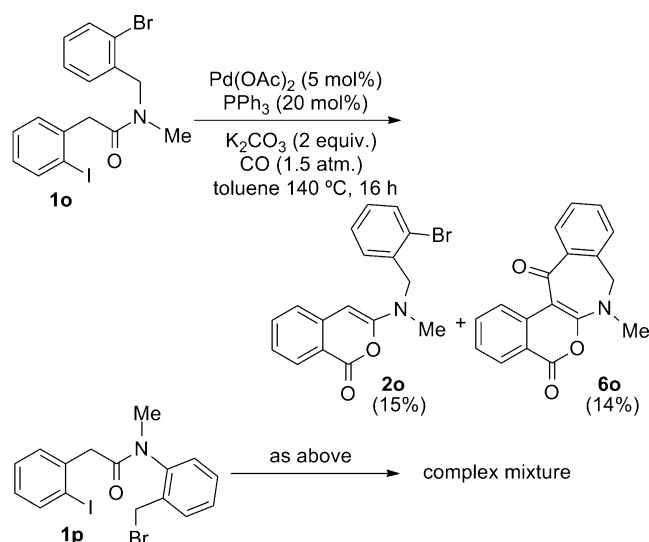
Next, we focused on the cascade reaction based on the initial formation of the isocoumarin core. When the *N*-arylated acetamide **1j** was submitted to the standard catalytic carbonylation conditions (1,4-dioxane at 100 °C) a small amount of the expected fused heterocycle **6j** was formed, along with a substantial amount of the isocoumarin derivative **2j** (Scheme 7).

We were pleased to observe an increase in the yield of the doubly carbonylated product **6j** to 60% when the reaction was performed in toluene at 140 °C (Scheme 8). The replacement of PPh<sub>3</sub> for other bidentate phosphine ligands such as dppe or dppf gave divergent results. While dppe hampered the second carbonylation, affording only traces of **6j** and a 12% of the indole derivative **7j**, dppf gave nearly the same results as those obtained with PPh<sub>3</sub>, 62% of the doubly carbonylated product **6j** and a small amount of **7j**. The cascade carbonylation could be extended to the substrates **1j–n**, which afforded the corresponding heterocycles **6j–6n** in moderate isolated yields, showing the tolerance of the reaction to both electron-donating and electron-withdrawing groups in the starting materials (Scheme 8). The required tertiary nature of the amides **1j–n** (for the reaction to proceed through the isocoumarin formation) could be accomplished with groups such as Me or Bn on the nitrogen atom. Along with the formation of compounds **6**, the reaction produced concomitantly a small amount of the indole derivatives **7**, which could be isolated and char-



**Scheme 8.** Catalytic cascade carbonylation of substrates **1j–n**.





**Scheme 9.** Carbonylation reaction of substrates leading to seven-membered rings.

acterized in the cases of the substrates **2l–n**. Noteworthy, the overall cascade double carbonylation reaction represents the breakage of two C–halogen and two C–H bonds in the substrates **1** giving rise to the formation of one C–O and three new C–C bonds present in the scaffolds **6**.

We also explored more challenging substrates which could potentially lead to seven-membered rings when submitted to the cascade carbonylation reaction. While the substrate **1o** afforded the expected polycyclic product **6o** in low yield (14%) along with the intermediate 3-aminoisocoumarin **2o**, the substrate **1p**, bearing a benzylic bromide moiety, gave a complex mixture of products (Scheme 9).

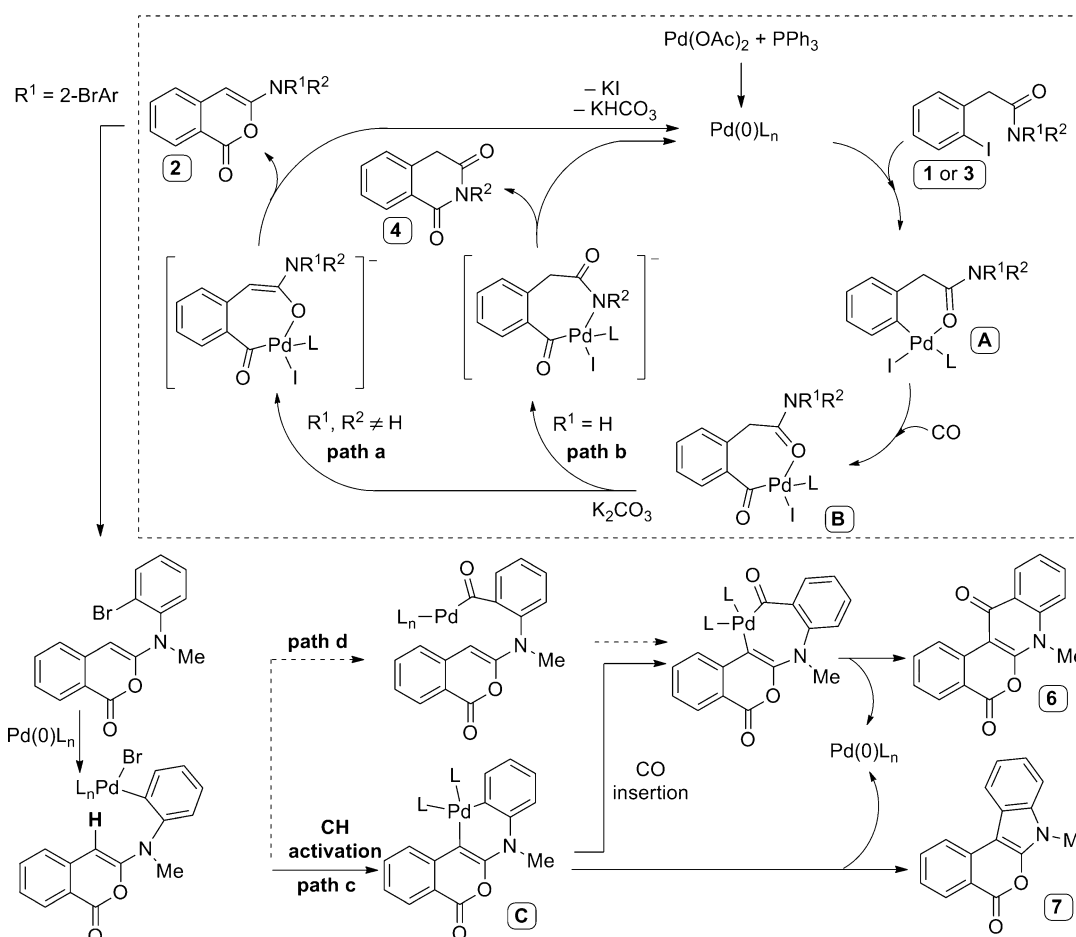
In order to confirm that isocoumarine **2** are the intermediates in the synthesis of the doubly carbonylated products **6**, the isocoumarin **2j** was submitted to the standard cascade carbonylation conditions with  $\text{Pd}(\text{OAc})_2/\text{PPh}_3$  in toluene at 140 °C for 12 h, affording a 45% yield of **6j** (Scheme 7). These results, along with the isolation of the indole derivatives **7j–n** in the reactions with substrates **2j–n**, strongly point toward a C–H activation step involving the alkenyl group present in the isocoumarine **2**.

Palladium-mediated or -catalyzed carbonylation reactions have become a powerful and versatile tool to introduce one carbonyl group in organic substrates.<sup>[37]</sup> Nevertheless, double carbonylation processes remain underexplored and are mainly restricted to a reduced number of transformations, the synthesis of  $\alpha$ -diketo derivatives being the most developed.<sup>[38]</sup> Remarkably, double carbonylation reactions involving C–H activation steps are exceptionally rare.<sup>[39]</sup>

Most likely, the reaction pathways followed by the two types of 2-arylacetamides **1** (tertiary amides) and

**3** (primary/secondary amides) in the carbonylation process share some common intermediates, which are depicted in Scheme 10. The oxidative addition to *in situ* generated Pd(0) species of the C–I bond present in the starting material would generate a six-membered intermediate palladacycle **A**, which could undergo the insertion of CO into the Pd–C bond leading to a Pd-acyl intermediate **B**. The participation of intermediates **A** and **B** in the reaction was confirmed by previous stoichiometric studies, where such compounds were isolated.<sup>[32]</sup> The decomposition pathway of the intermediate **B** depends on the degree of substitution on the nitrogen atom. When the starting amide is tertiary, the formation of the C–N bond is disfavoured. Instead, the presence of acidic protons in the  $\alpha$  position to the amide moiety enables the formation of an enolate intermediate which evolves through an oxidative C–O bond formation, leading to 3-aminoisocoumarins **2** (path a, Scheme 10). In the case of primary and secondary 2-arylacetamides, the C–N bond formation is preferred, giving rise to homophthalimide derivatives **4** (path b, Scheme 10). The substrates **1j–n** (bearing the 2-bromoaryl substituent on the nitrogen atom) could undergo a further oxidative addition to Pd(0), placing the resulting Pd(II) atom in a privileged position to activate the alkenyl C–H bond of the isocoumarin core (path c, Scheme 10) to afford the six-membered C,C-palladacycle **C**. This intermediate could undergo the reductive elimination of Pd(0) with subsequent formation of the indole derivatives **7**. Nevertheless, CO insertion into any of the C–Pd bonds of palladacycle **C** may happen preferentially prior to the reductive elimination step, producing the fused heterocycles **6**. Alternatively, the CO insertion step could also take place before the C–H activation event (path d, Scheme 10). The formation of the indole derivatives **7** might possibly be minored in favour of the heterocycles **6** under high CO pressure conditions. An additional reaction pathway involving a Heck-type palladation of the alkenyl moiety of the *N*-2-bromoarylisocoumarins **2** by Pd(II) species cannot completely be ruled out, however it seems less probable since it would imply the further oxidative addition of the C–Br bond to give a Pd(IV) intermediate, which could later undergo the CO insertion.

In summary, we have developed the palladium-catalyzed carbonylation reaction of 2-(2-iodoaryl)acetamides, extendable to esters and thioesters. This synthetic methodology enables the use of CO as a cheap  $\text{C}_1$  feedstock in the synthesis of homophthalimides and 3-aminoisocoumarins, depending on whether the starting material is a primary/secondary or tertiary ary-lacetamide. These carbonylation reactions constitute a new way to introduce N-, O- and S-substituents in the isocoumarin scaffold. Moreover, conveniently designed ary-lacetamides allow the performance of cas-



**Scheme 10.** Possible reaction pathway for the synthesis of 3-aminoisocoumarins **2**, homophthalimides **4** and the doubly carbonylated products **6**.

cade double carbonylations involving the activation of the alkenyl C–H moiety present in the 3-substituted isocoumarin core, affording interesting fused heterocycles.

## Experimental Section

### Representative Procedure for the Synthesis of Iso-coumarin and Homophthalimide Derivatives **2** and **4**

A Carius tube was charged with the starting acetamide (**1** or **3**) (0.6 mmol, 1 equiv.),  $K_2CO_3$  (83 mg, 0.6 mmol, 1 equiv.),  $Pd(OAc)_2$  (7 mg, 0.03 mmol, 5 mol%),  $PPh_3$  (32 mg, 0.122 mmol, 20 mol%) and a teflon-coated stirrer bar. Three vacuum-nitrogen cycles were applied to the tube and dry 1,4-dioxane (3 mL) was added. The tube was evacuated, re-filled with CO (1.2 atm.) and sealed. The reaction mixture was heated in an oil bath at 100 °C for 16 h. After cooling the Carius tube to room temperature, the reaction mixture was diluted with EtOAc (30 mL) and filtered through a Celite pad. The filtrate was concentrated and the crude product was purified by column chromatography.

### Representative Procedure for the Synthesis of Derivatives **6**

A Carius tube was charged with *N*-arylacetamide (**1**) (0.5 mmol, 1 equiv.),  $K_2CO_3$  (140 mg, 1 mmol, 2 equiv.),  $Pd(OAc)_2$  (6 mg, 0.026 mmol, 5 mol%),  $PPh_3$  (26 mg, 0.099 mmol, 20 mol%) and a teflon-coated stirrer bar. Three vacuum-nitrogen cycles were applied to the tube and dry toluene (3 mL) was added. The tube was evacuated, refilled with CO (1.5 atm.) and sealed. The reaction mixture was heated in an oil bath at 140 °C for 16 h. After cooling the Carius tube to room temperature, the reaction mixture was diluted with  $CH_2Cl_2$  (150 mL) and filtered through a Celite pad. The filtrate was concentrated to ca. 2 mL and the crude material was purified either by column chromatography or fractional crystallization.

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**10** 2-Arylacetamides as Versatile Precursors for 3-Aminoisocoumarin and Homophthalimide Derivatives: Palladium-Catalyzed Cascade Double Carbonylation Reactions

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